Effect of Dietary Countermeasures and Impact of Gravity on Renal Calculi Size Distributions Predicted by PBE-System and PBE-CFD Models

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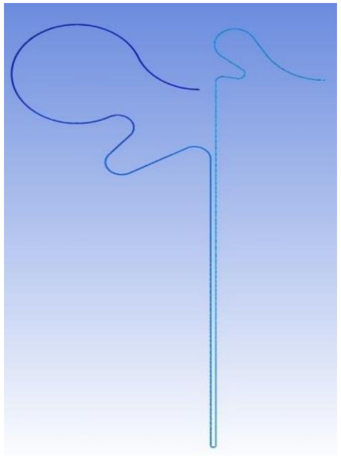
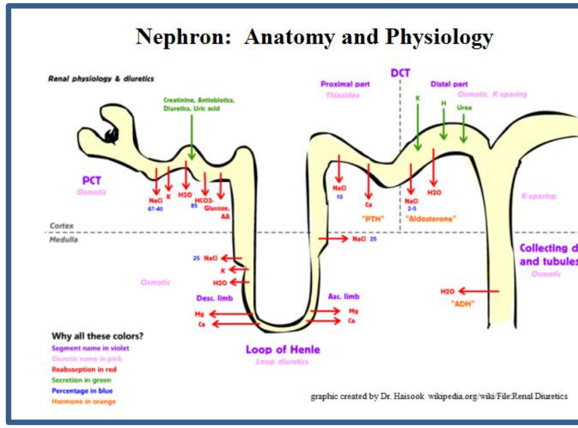
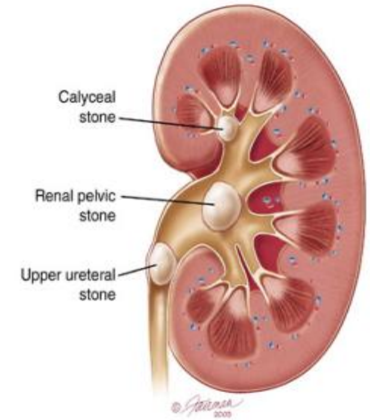
System & Multiphase CFD Models for Renal Stone Development & Transport in 1G and Microgravity







Renal Stone Formation Model (RSFM) was developed to address important NASA questions/needs in support of IMM:

- Evaluate the risk of developing a critical renal stone incident during long duration microgravity missions based *on available astronaut biochemical data*
- Assess efficacy of countermeasures such as
  - Increase Hydration
  - Potassium Citrate & Magnesium
- Perform "*what if*" parametric studies to understand and assess risk of developing renal stone upon entry into a 1g or a remote partial gravitational field such as Mars or Moon where relevant astronaut biochemical data is unavailable

Renal Stone Population Balance (PBE) System Model: Nucleation, Growth & Agglomeration

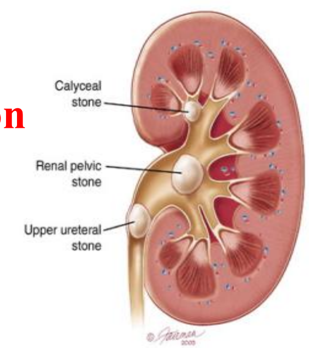
Population Balance Equation:

$$\frac{n(D)}{\tau} + \underbrace{G_D \frac{\partial n(D)}{\partial D}}_{\text{Growth}} = \underbrace{\int_0^{D/2} \beta n(D - D')n(D')dD'}_{\text{Agglomeration-Birth}} - \underbrace{n(D)\int_0^{\infty} \beta n(D')dD'}_{\text{Agglomeration-Death}}$$

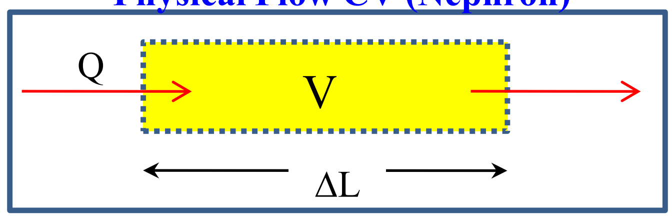
Nucleation BC:

$$n\ (D = 0) = n^o = {B^o}/{G_D}$$

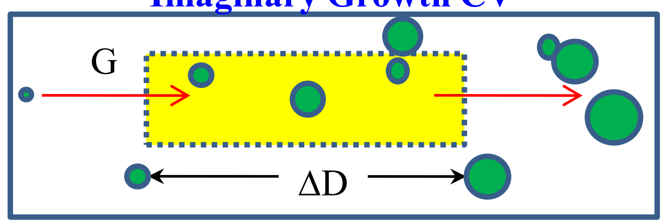
Kidney:
Mixed Suspension
Mixed Product
Removal
Crystallizer

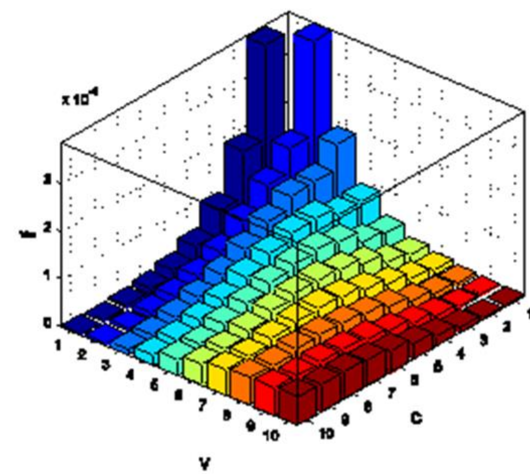


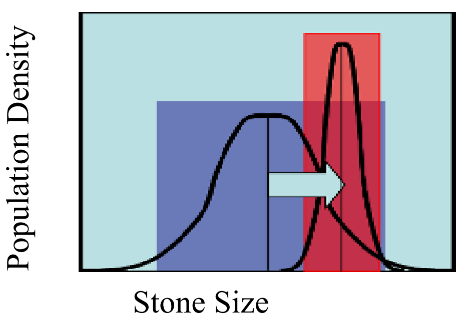
Physical Flow CV (Nephron)



Imaginary Growth CV







Relative Supersaturation:

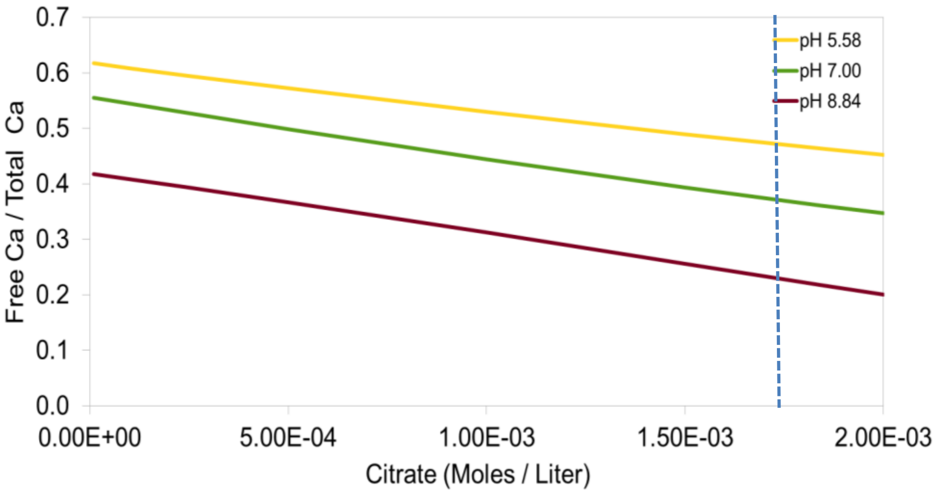
$$RSS = \left[\frac{C_{ca,\infty}\ C_{ox,\infty}\ f_2^2}{K_{so}}\right]^{1/2} \quad (2)$$

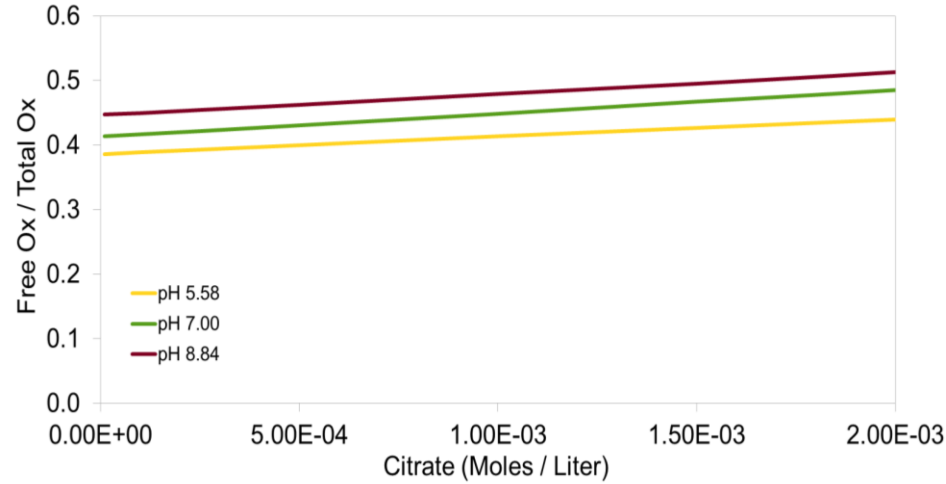
Inhibition: Citrate, Pyrophosphare, Hydration

- ***Direct*** : K_B , K_D , β , τ
- ***Indirect*** : ***RSS***

Jess: Effect of Direct Inhibition by Speciation on the Urinary CaOx Supersaturation

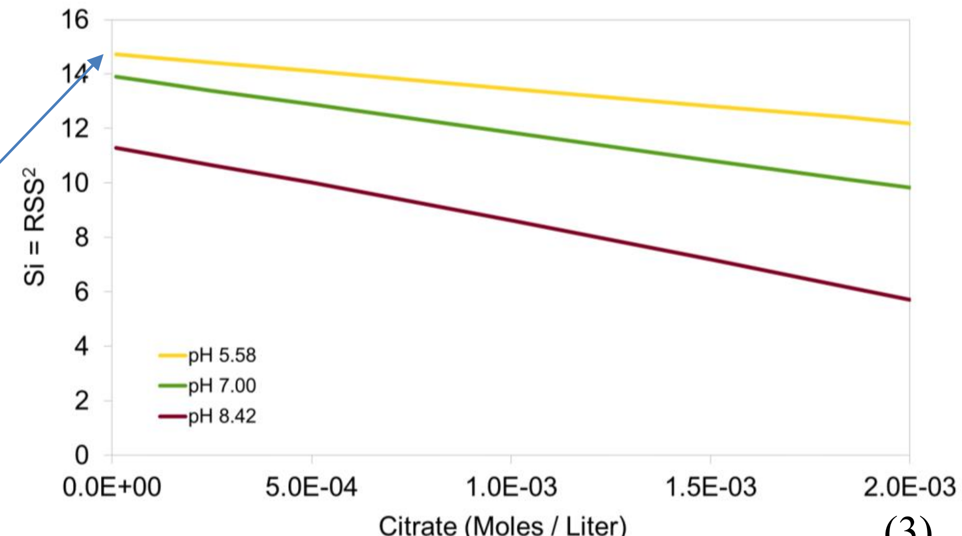
❖ **Microgravity Astronaut:** Average of 24-urine excretion rates obtained from 86 astronauts on the day of landing. (Whitson et al.[36])





Due to speciation with other than citrate urine is about 38% inhibited wrt Ca and about 62% inhibited wrt Ox

Si: ~ 32 ➔ 15



Coupling the PBE Model to JESS Speciation Code: Effect of Direct and Indirect Urinary Inhibition

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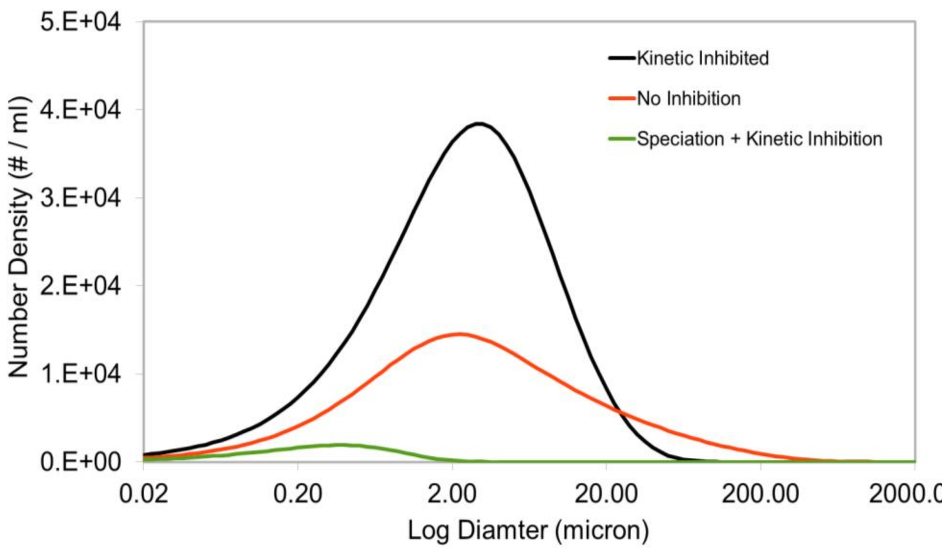
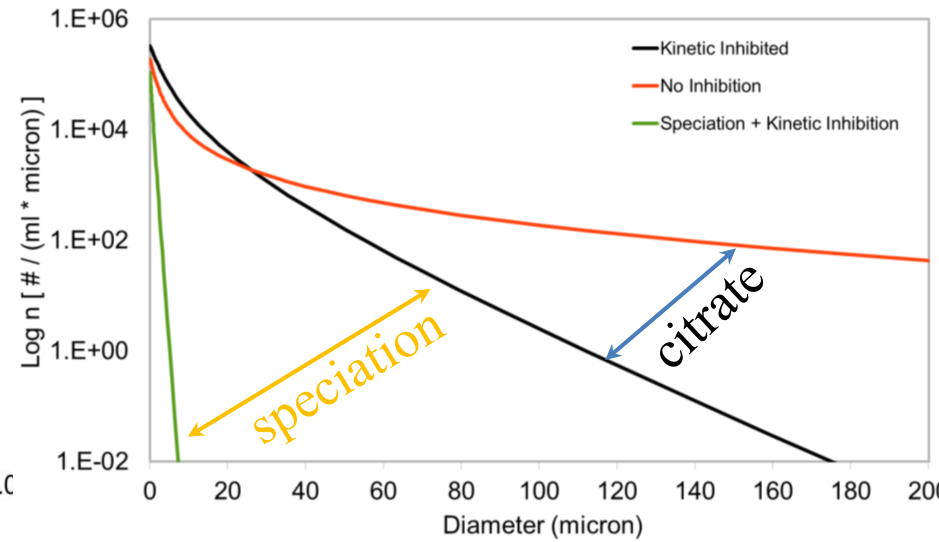
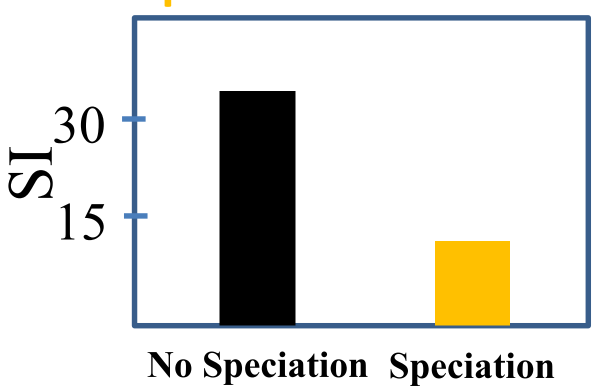




Speciation Inhibition



Meyers & Smith (1975)

Kok & Khan (1990)

Citrate Kinetic Inhibition

	Kg (m/s)	Kb (#/m³sec)	Beta (m³/s)
No Inhibition	5.9E-10	5.9E+07	2.78E-14
Kinetic Inhibition	5.9E-11	5.9E+06	1.50E-15

(4)

Coupling the PBE Model to JESS Speciation Code: Effect of Direct and Indirect Urinary Inhibition

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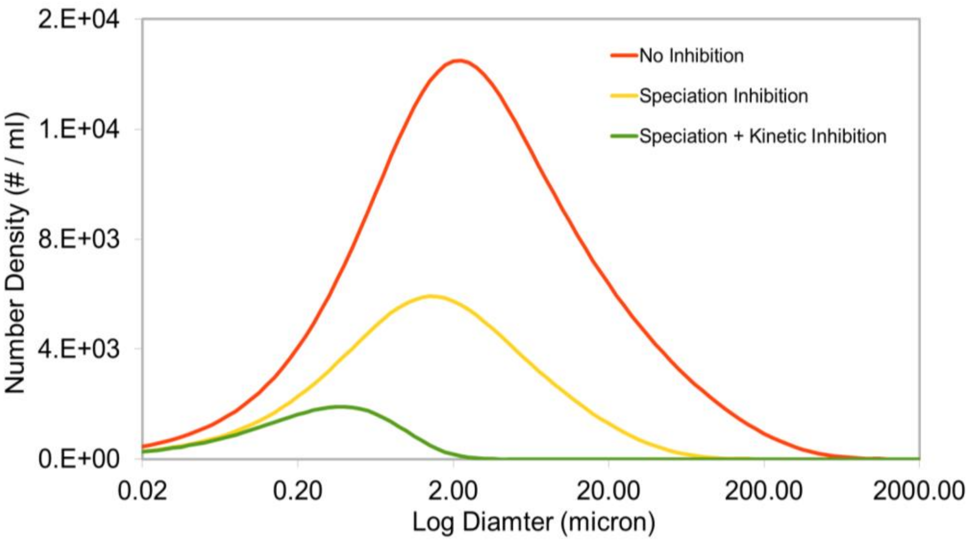
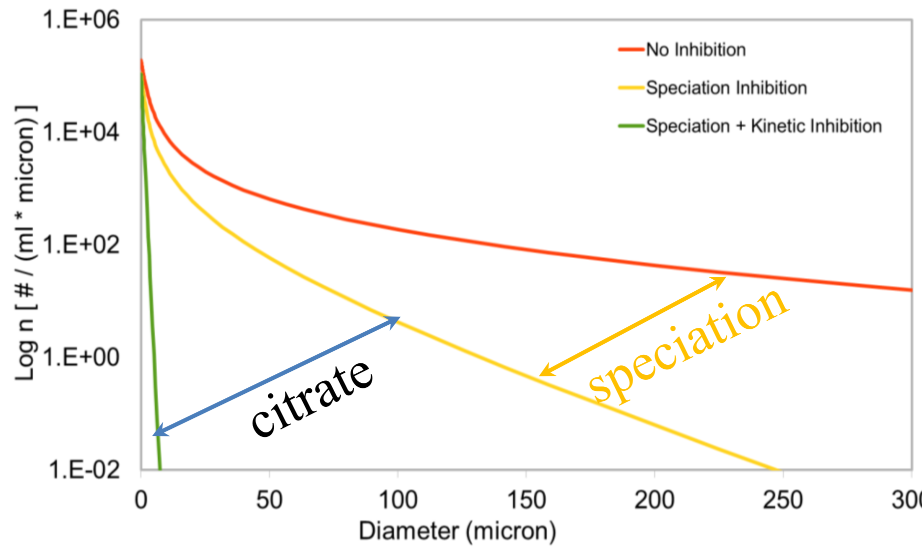
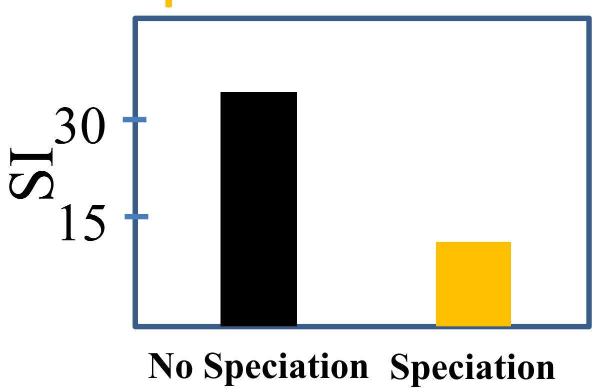




Speciation Inhibition



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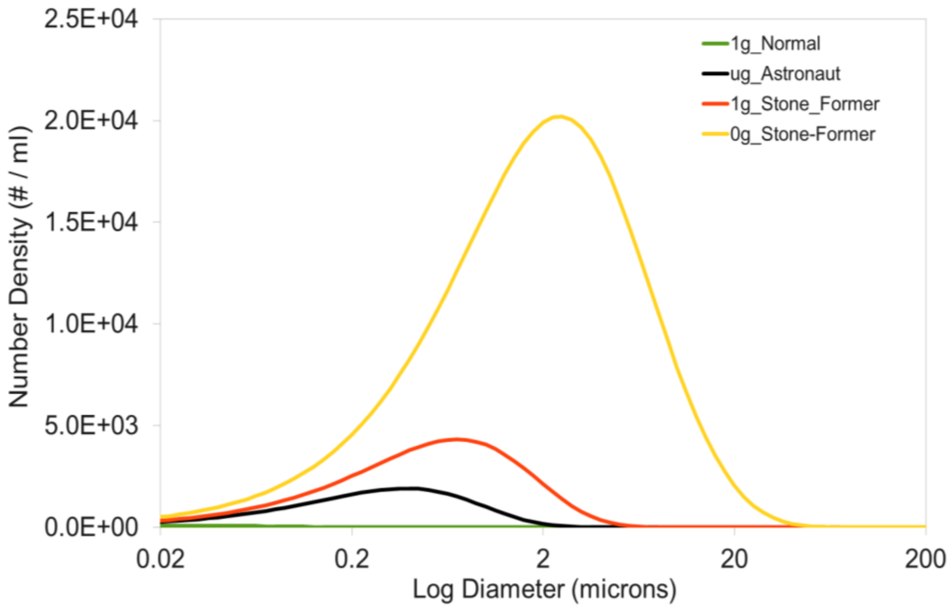
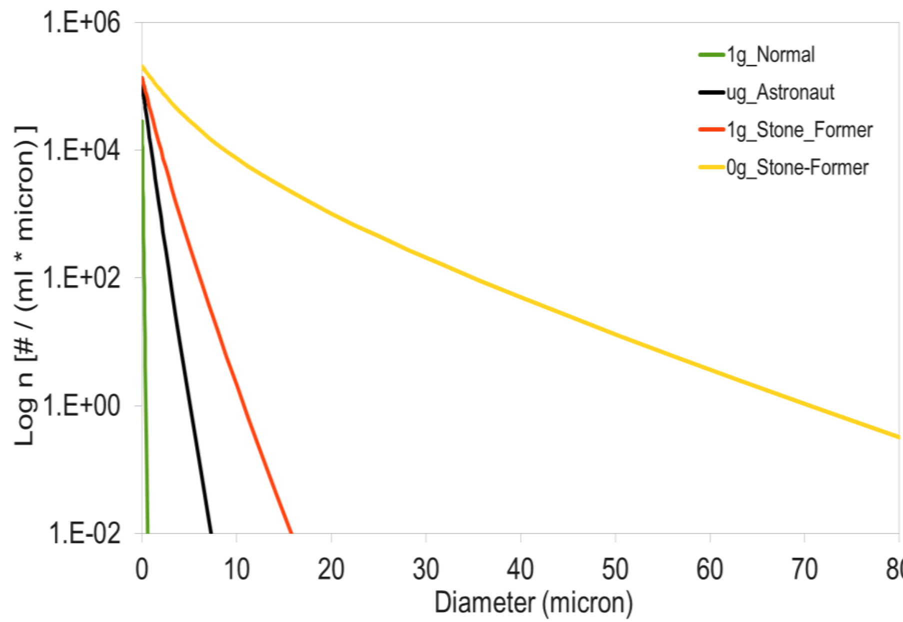
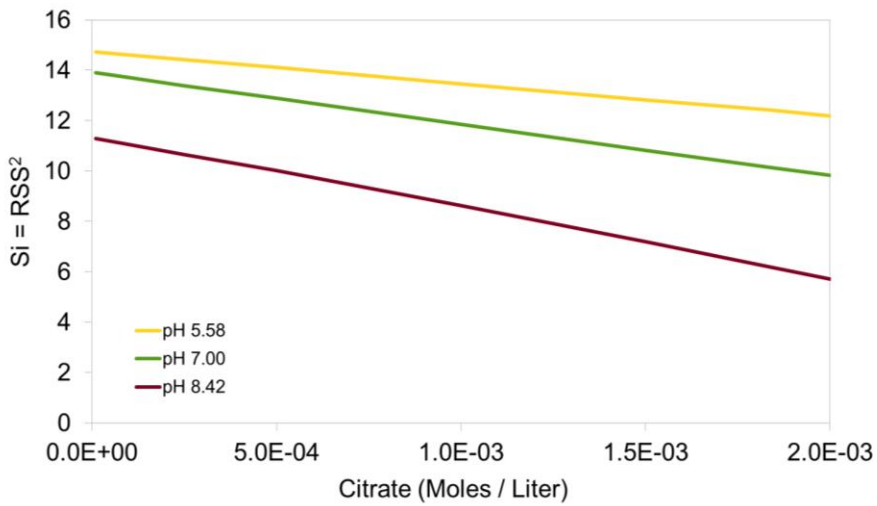
Prediction Renal Calculi Size Distribution for The 4 Subject Test Cases

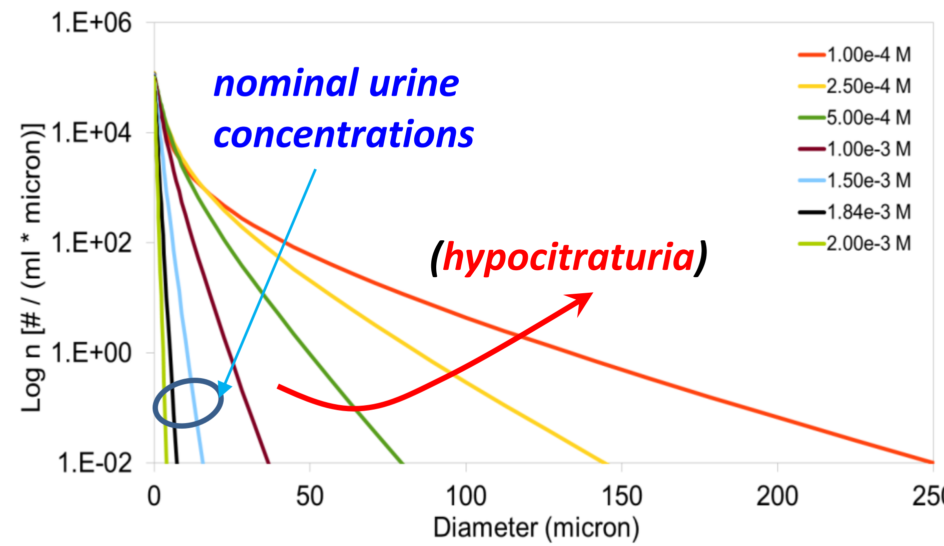


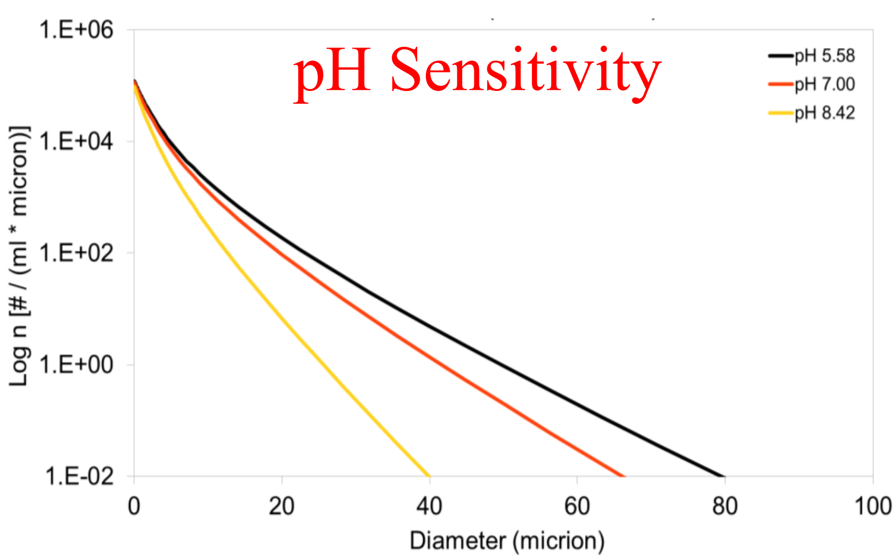


- **1G Normal**: 24 urine sample Mineral Metabolism Laboratory at University of Texas Southwestern Medical Center UTSW.
- **1G Stone-former**: 24 Urine Sample (Robertson et al., Laube et al.)
- **Microgravity Astronaut:** Average of 24-urine excretion rates obtained from 86 astronauts on the day of landing. (Whitson et al.)
- **Microgravity Stone Former:** *Hypothetical* worst case scenario constructed using the long duration 24-urine data R+2 (Whitson et al.)

Dietary Countermeasures for Microgravity Astronaut Subject: Effect of Citrate

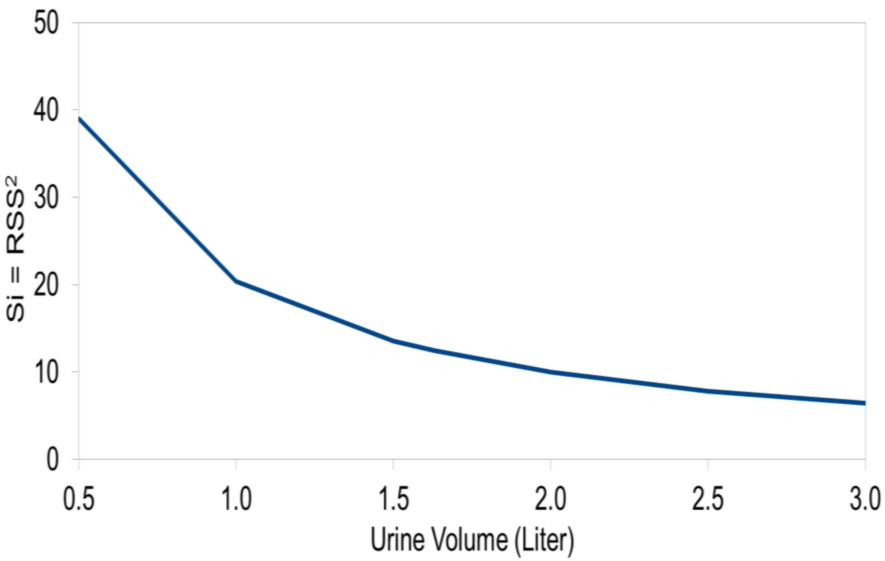


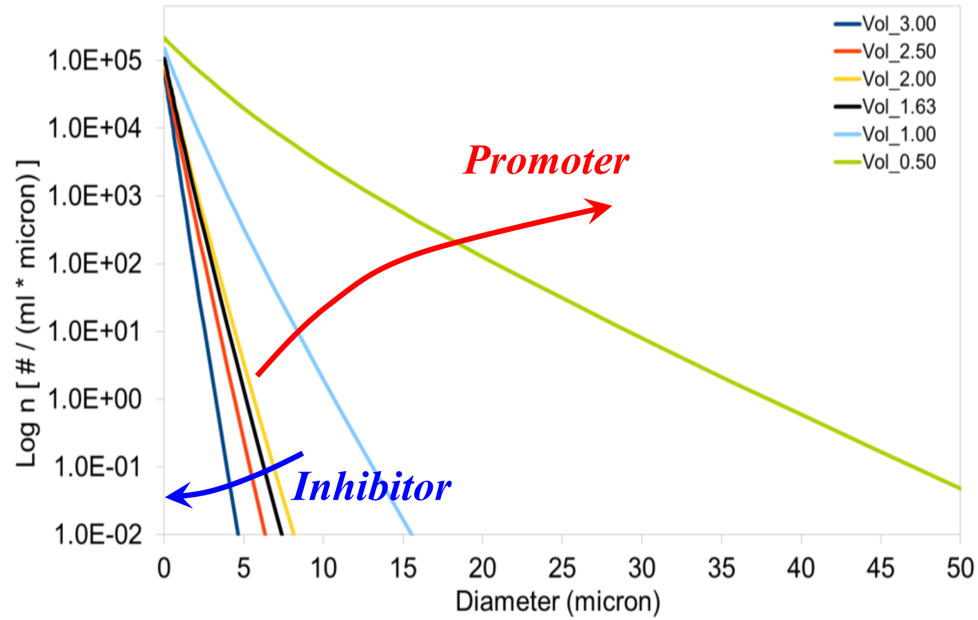




Reduction of kinetic inhibition at below normal citrate concentrations ➔ drastic increase in the risk of renal stone formation

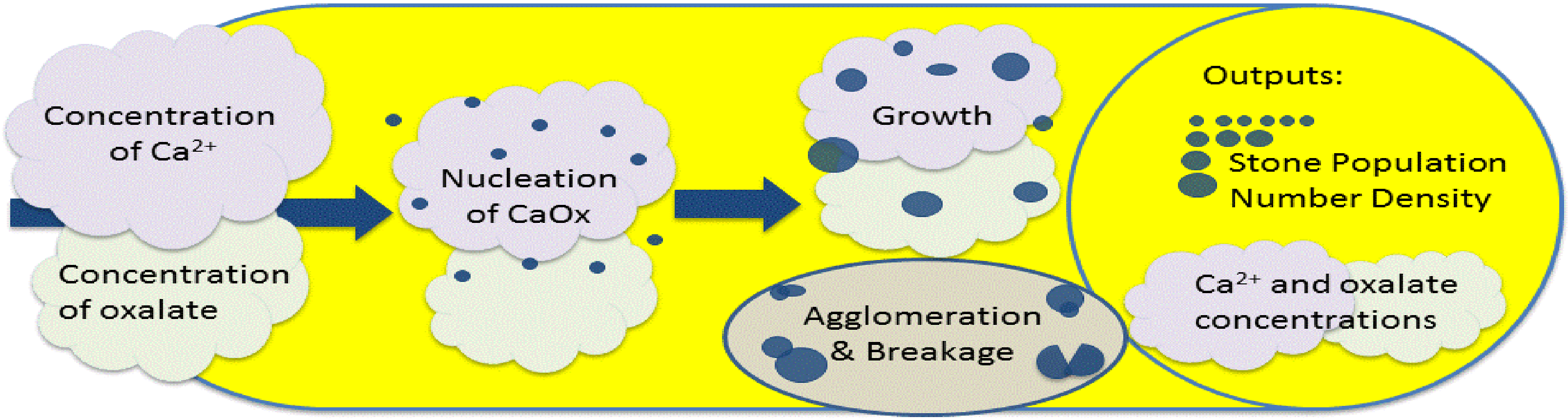
Effect of Dietary Countermeasures for Microgravity Astronaut Subject: Effect of Hydration





- Decrease in urine volume is a powerful promoter
- Volume above 2 liters /day is recommended

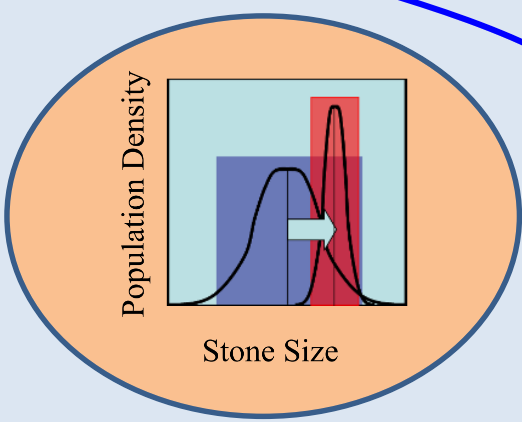
G Effect: Coupling Stone PBE to Urinary Flow & Ca and Ox Transport in the Nephron



Population Balance Equation Coupled to Urinary Flow & Species Transport

$$\frac{\partial}{\partial t}[n(V,t)] + \nabla\cdot[\vec{u}n(V,t)] + \underbrace{\nabla_v\cdot[G_v n(V,t)]}_{\text{Growth term}} = \underbrace{\frac{1}{2}\int_0^V a(V-V',V')n(V-V',t)n(V',t)dV'}_{\text{Birth due to Aggregation}} - \underbrace{\int_0^\infty a(V,V')n(V,t)n(V',t)dV'}_{\text{Death due to Aggregation}}$$

$$+ \underbrace{\int_{\Omega_v} \nu g(V')\beta(V \mid V')n(V',t)dV'}_{\text{Birth due to Breakage}} - \underbrace{g(V)n(V,t)}_{\text{Death due to Breakage}} \qquad (8)$$

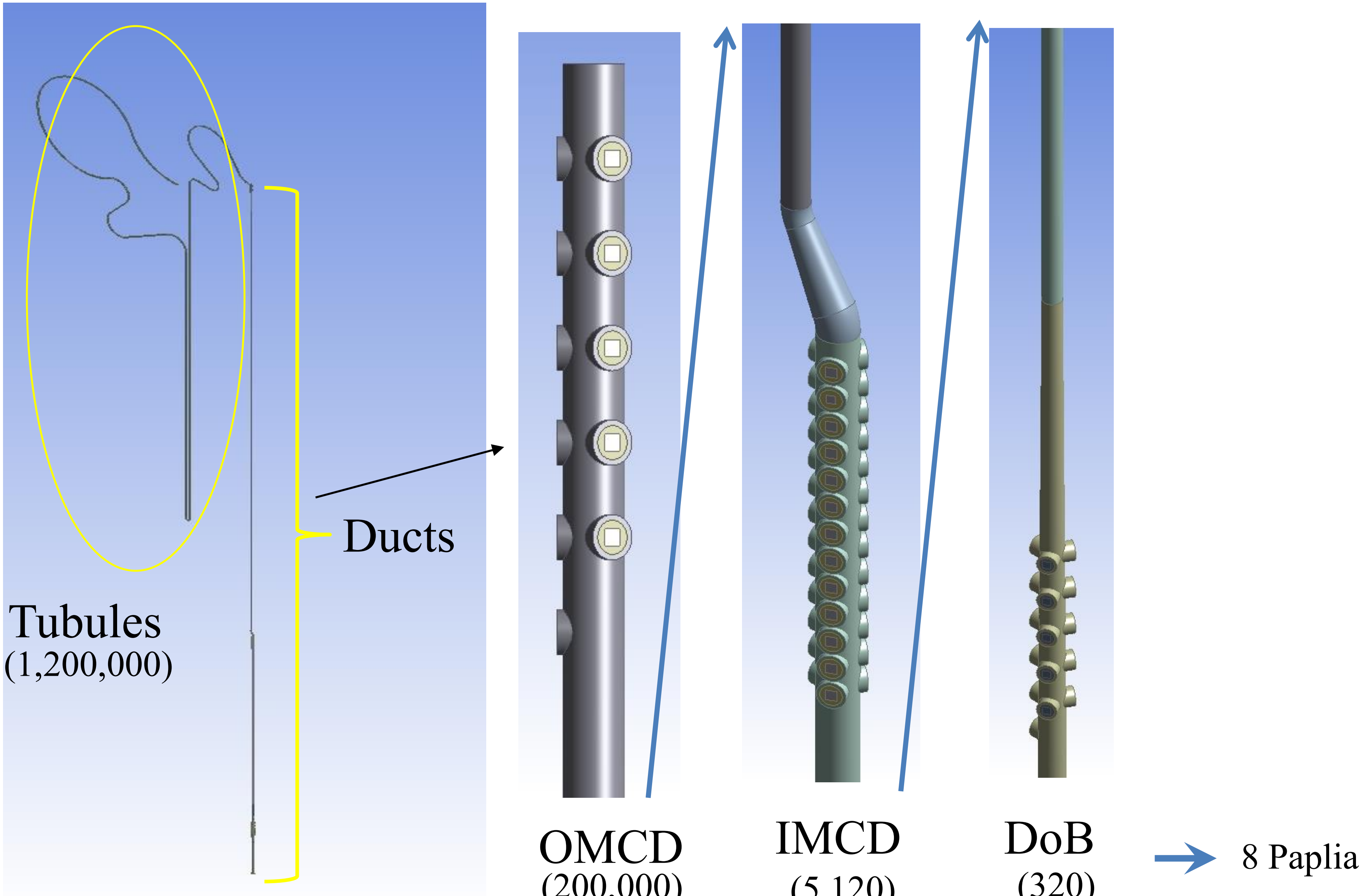


$G_v = dV/dt$

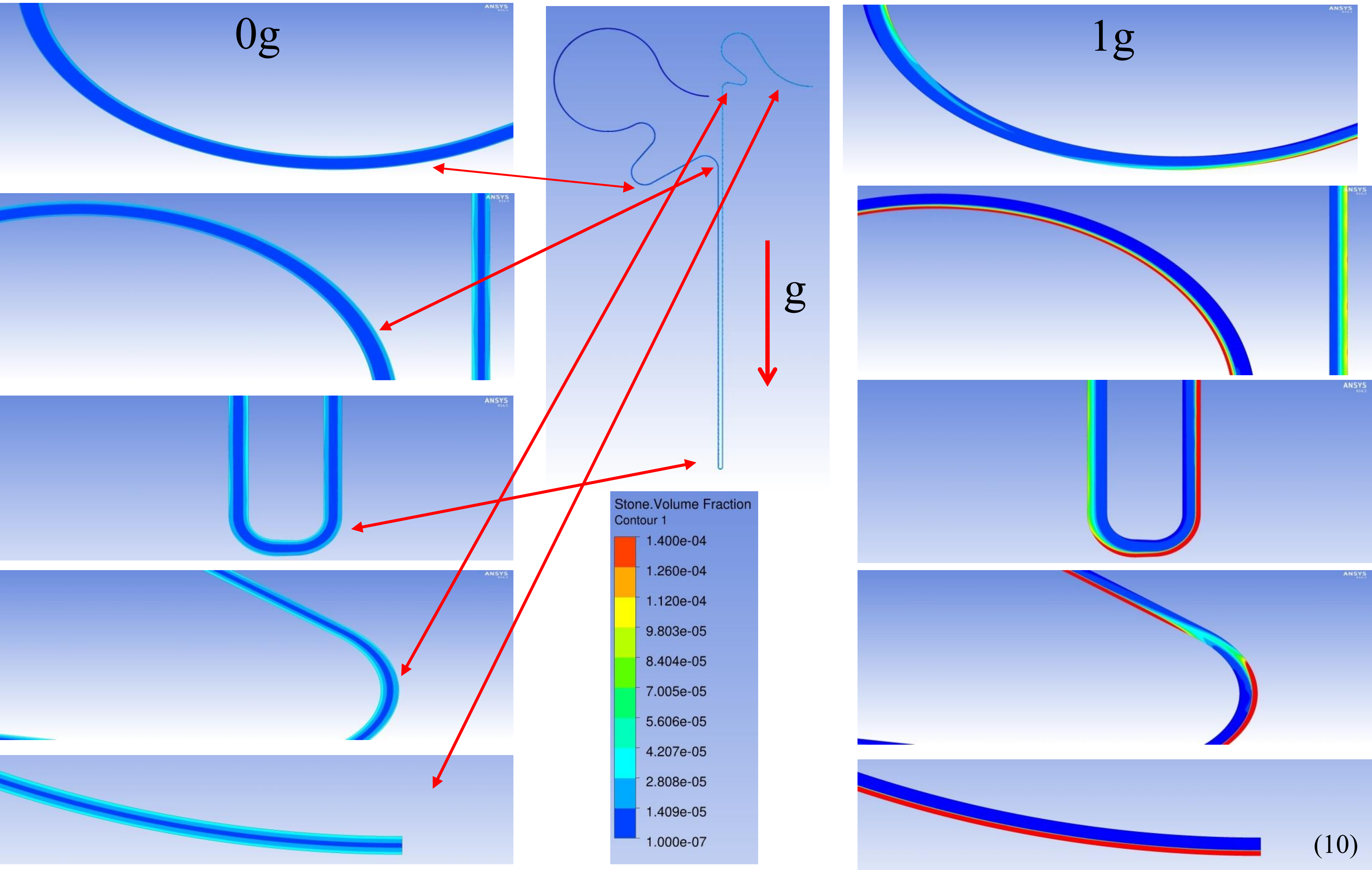
ANSYS/FLUENT CFD Code

- Momentum Equation
- Species Transport Equation

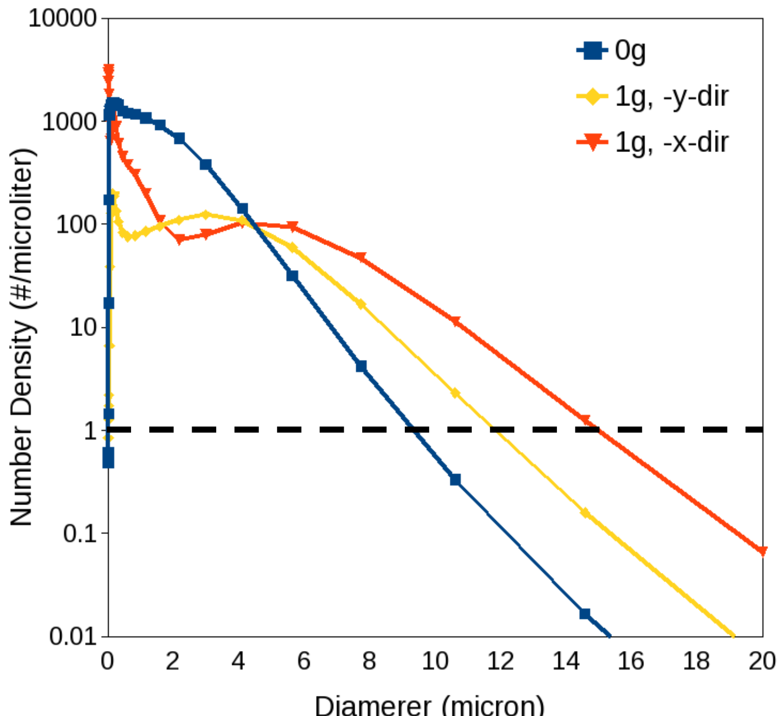
Realistic 3D Nephron Geometry

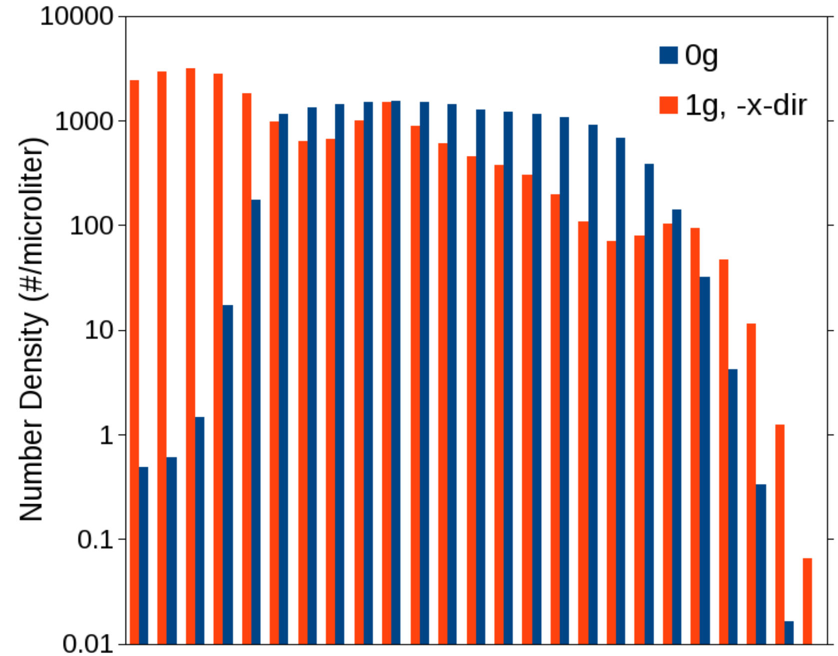


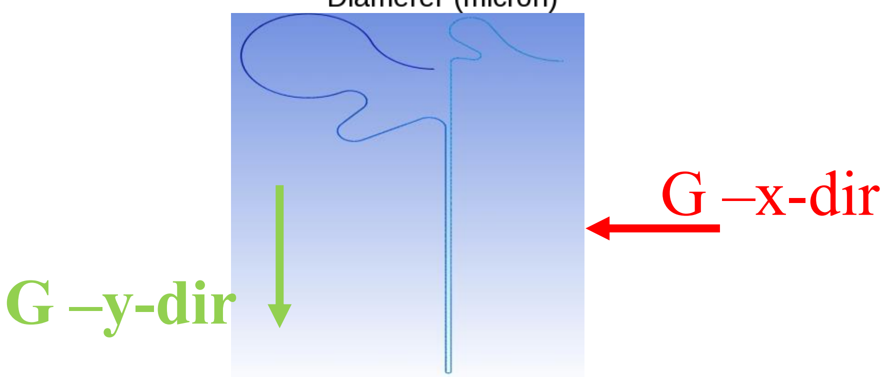
Effect of Gravity on Stone Transit through Nephron

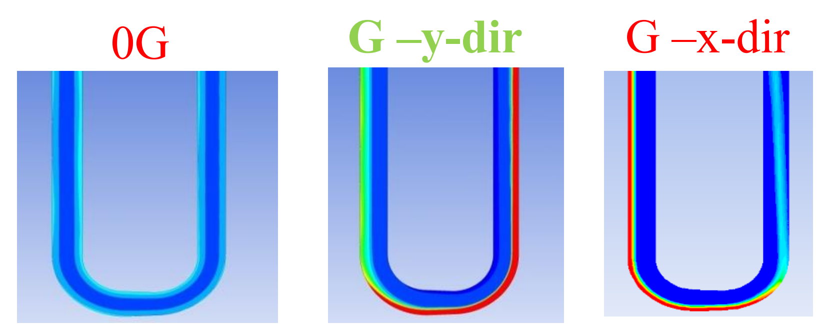


Effect of Gravity on Stone Size Distribution in 3D Nephron Simulations





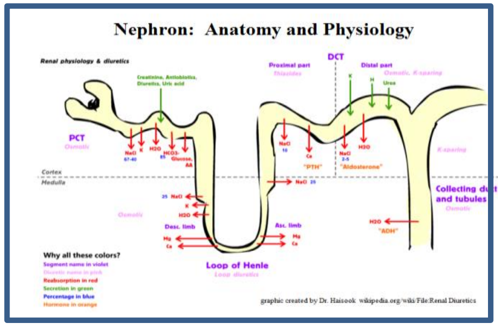




CFD results are in conformity with recent CT scans indicating CaOx Randal plaque formation: Coe & Evans et al, 2015; Williams & McAteer, 2012 ; Kim et al, 2005.

Closure & Future Path

- Numerical prediction show a normal astronaut is subject to increased but subcritical risk mainly due to sufficient direct and indirect urinary inhibition
- Citrate treatment and hydration to provide urinary volumes above 2 liters/day were found to be both necessary and effective dietary countermeasures
- **Results seem to indicate that investment in finding appropriate direct kinetic inhibitors such as citrate, pyrophosphate, etc. is maybe more impactful than attempts to increase indirect inhibition by speciation.**
- The effect of variation in Ca, Ox variations in various sections of the nephron is currently being incorporated into the 3D CFD Model. This enables exploration of the following questions:
  - Does the initial (acute) impact of microgravity on Nephron biochemistry raise the risk of stone development?
  - What is the impact of Artificial Gravity (AG) on renal stone development



Extra slides

RSFM Model Development Flow Chart